

CLINICAL REPORT

Family still matters: Counseling patients with complex family histories of colon and endometrial cancers

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Abstract

Background: There are no national guidelines for the management of patients with a family history consistent with Lynch syndrome (LS) but a negative genetic test. To determine current management practices, genetic counselors' (GCs) recommendations were assessed.

Methods: A survey of GCs using five hypothetical pedigrees was posted to National Society of Genetic Counselors (NSGC) discussion forums. Descriptive statistics were used.

Results: One-hundred and fifteen surveys were completed. A pedigree with a first-degree relative (FDR) with early-onset colorectal cancer (CRC) and a family history of CRC and endometrial cancer (EC) prompted 83% ($n = 95$) of respondents to recommend early and frequent colonoscopies, based on family history. When the CRCs and ECs occurred in family members removed from the proband, 96% ($n = 110$) of GCs said they would screen based on family history. However, only 52% ($n = 60$) suggested CRC screening should begin earlier and occur more often, and 43% ($n = 50$) suggested CRC screening should follow standard age and frequency guidelines.

Conclusion: Concordance of opinion among GCs for the management of patients with negative genetic test results exists when FDRs are affected. However, when affected relatives are more distant, GCs disagreed on screening recommendations. These data suggest a need for guidelines for patients with a family history of cancer and a negative genetic test.

KEYWORDS

colon cancer, endometrial cancer, genetic counseling, Lynch syndrome, management guidelines

1 | INTRODUCTION

Lynch syndrome (LS), caused by germline pathogenic variants in the mismatch repair (MMR) genes *MLH1* (OMIM: 120436), *MSH2* (OMIM: 609309), *MSH6* (OMIM: 600678),

PMS2 (OMIM: 600259), or *EPCAM* (OMIM: 185535), is the most common known cause of hereditary colorectal cancer (CRC), affecting approximately 3% of all patients with CRC (Hampel et al., 2005, 2008). Individuals with LS are at an increased risk for other cancers including endometrial

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cancer (EC) and ovarian cancer, and benefit from intensive cancer surveillance and/or prophylactic risk reduction surgeries (Bonadona, Bonaiti, & Olschwang, 2011; Järvinen et al., 2000; Schmeler et al., 2006). Traditional methods to identify patients at risk for LS, based on family histories of cancer, such as Amsterdam II criteria and revised Bethesda Guidelines, have a low sensitivity (Barnetson et al., 2006; Hampel et al., 2008; Haraldsdottir et al., 2014; Pearlman et al., 2017; Umar et al., 2004; Vasen, 2000; Vasen, Watson, Mecklin, & Lynch, 1999). More recently, the National Comprehensive Cancer Network (NCCN) revised family history of cancer criteria for testing for LS; many clinicians now use these revised criteria (Gupta et al., 2017).

While management guidelines exist for patients identified as having a germline LS pathogenic variant (Gupta et al., 2017), consensus guidelines for the management of patients who meet LS testing criteria but who have negative germline testing are nonexistent. As per the NCCN, management of patients who are not tested, or for whom no pathogenic variants, or a variant of unknown significance is found should include, “tailored surveillance based on individual and family risk assessment.” Historically, the presence or absence of MMR proteins in the tumor was used to aid in clinicians’ suspicion of LS, which in turn helped guide management recommendations. The field of genetics thus developed terms such as “Lynch-like,” “Uninformative Lynch,” and “Familial Colorectal Cancer Syndrome Type X” to help delineate and assign appropriate screening recommendations for these families (Boland, 2013; Lindor et al., 2005; Rodriguez-Soler et al., 2013). However, with the recent advent of new tumor next-generation sequencing (NGS) technologies, the genetics community is steering away from using such terms to help manage patients.

For many affected patients with abnormal immunohistochemical (IHC) staining for the MMR proteins, or microsatellite instability (MSI), the recent availability of tumor testing for somatically acquired pathogenic variants has helped clarify management (Latham, Srinivasan, & Kemel, 2018). Mounting evidence indicates that many individuals with MMR-deficient tumors and negative germline testing have two somatically acquired pathogenic variants in a MMR gene, and therefore do not have LS (Haraldsdottir et al., 2014; Mensenkamp et al., 2014; Sourrouille et al., 2013). The NCCN does not recommend following these patients with the rigorous surveillance of early and frequent colonoscopies and protective surgeries.

Population-based LS screening, a tier 1 guideline by The Centers for Disease Control and Prevention, will frequently identify individuals with negative genetic testing and family histories suggestive of LS. Despite the new opportunities to help characterize families suggestive of LS without germline MMR pathogenic variants, tumor tissue or tumor testing is not always available to clarify risks. Additionally,

the most informative family member for testing may not be available, leaving clinicians to make management recommendations for unaffected family members. Because surveillance recommendations for LS include rigorous screening and preventive surgeries, overmanaging these families can cause harm and present an unnecessary cost burden on the health care system. (Areia et al., 2019; Cross et al., 2018; Kim, Kim, & Park, 2019) Thus, there is a need to address the management of patients with complex family histories that meet LS evaluation guidelines, but have a negative germline genetic test. To begin to address this, we studied current practices by assessing genetic counselors’ (GCs) management recommendations for patients with negative genetic testing and a family history suggestive of LS.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

Protocol of this study was performed under the approval of the University of Texas Southwestern Institutional Review Board (STU # 032018-012).

2.2 | Instrumentation

The authors developed a survey, based on previous NCCN clinical testing criteria for LS (Amsterdam II criteria and revised Bethesda Guidelines) and clinical experience. A draft of the survey was piloted by 16 cancer GCs. Their feedback resulted in minor revisions, including adding government organization as an option for type of work institution and adding an optional free response section to explain answer rationale for each pedigree. The online survey was administered through Redcap and consisted of four sections. Section 1 surveyed the demographics of the study population. Section 2 included five hypothetical pedigrees (Figure 1), generated with *CancerGeneConnect*. All pedigrees included an unaffected 30-year-old female proband with negative comprehensive genetic testing, and a family history of CRC and/or EC suggestive of LS. For consistency, all family members were deceased and participants were informed that no genetic testing was performed prior to their death. Each hypothetical pedigree was followed by three multiple-choice questions assessing CRC risk management, EC risk management, and extra-colonic risk management (Table 1); an optional open-ended response was available for participants to explain their rationale. Section 3 asked respondents to choose the most appropriate provider to make screening recommendations for individuals with a negative genetic test result and a family history consistent with LS. Section 4 allowed for free response of additional comments.

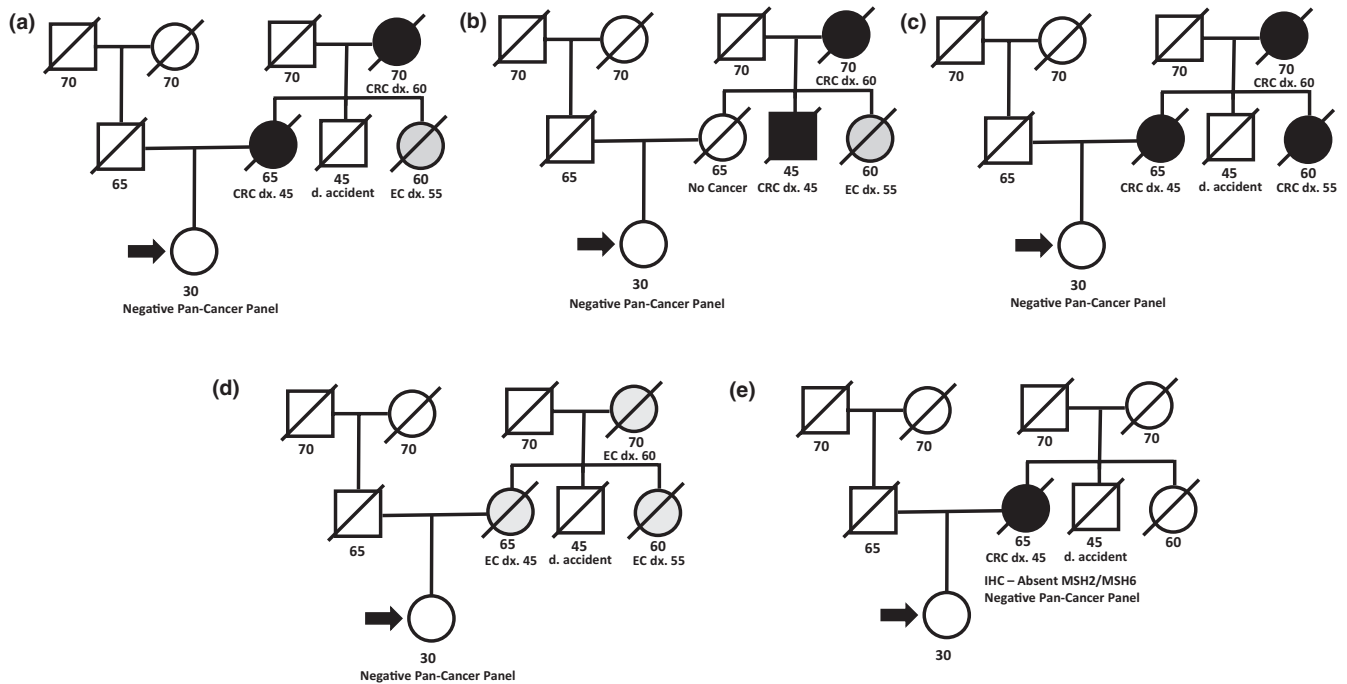


FIGURE 1 Five hypothetical pedigrees. All pedigrees included an unaffected 30-year-old female proband with negative comprehensive genetic testing, and a family history of colorectal cancer (CRC) and/or endometrial cancer (EC) suggestive of Lynch syndrome. (a) First-degree relative with CRC and a family history of CRC and EC meeting Amsterdam II criteria. (b) Second-degree relative with CRC and family history of CRC and EC meeting Amsterdam II criteria. (c) First-degree relative with CRC and family history of CRC meeting Amsterdam I criteria. (d) First-degree relative with EC and family history of EC meeting Amsterdam II criteria. (e) First-degree relative with CRC whose tumor had absent staining for the MSH2/MSH6 proteins

TABLE 1 National Comprehensive Cancer Network (NCCN) Lynch syndrome guidelines (v3.2018), NCCN family-history-based management guidelines (v3.2018), and study multiple-choice questions assessing colorectal cancer (CRC) and endometrial cancer risk management

	Lynch syndrome management guidelines	NCCN family-history-based guidelines	Survey multiple choice options
Colon cancer	<ul style="list-style-type: none"> Begin colonoscopy at 20–25 years, repeat every 1–2 years 	<ul style="list-style-type: none"> First-degree relative with CRC: Begin colonoscopy at 40 years or 10 years before earliest diagnosis of colon cancer, repeat every 5–10 years Second-degree relative with CRC: Begin colonoscopy at 50 years 	<ol style="list-style-type: none"> Begin colonoscopy at 20–25 years, repeat every 1–2 years Begin colonoscopy at 35 years, repeat every 5–10 years Begin colonoscopy at 50 years, repeat every 5–10 years
Endometrial cancer	<ul style="list-style-type: none"> Consider screening via endometrial biopsy every 1–2 years and/or transvaginal ultrasound and consider hysterectomy after childbearing is complete 	<ul style="list-style-type: none"> No guidelines 	<ol style="list-style-type: none"> Consider screening via endometrial biopsy every 1–2 years and/or transvaginal ultrasound and consider hysterectomy after childbearing is complete No specific recommendations

2.3 | Participants and procedures

An invitation containing an overview of the study and a link to an online survey was posted to the NSGC Cancer Special Interest Group (SIG) and the NSGC general discussion forum. Participants had 2 weeks from the initial invitation to complete the survey; a study reminder was reposted 1 week after the initial invitation. Inclusion criteria for the study included board-eligible or board-certified GCs who are

members of the NSGC, at least 18 years of age, and able to read in English. Participants who completed the survey in full were eligible to enter an anonymous raffle to win one of eight \$25 Amazon gift cards.

A total of 161 surveys were returned. As it is unknown how many NSGC members subscribe to the Cancer SIG or general discussion forum, a response rate was not calculated. Of the 161 returned surveys, 115 were completed in full (71.4% completion rate) and these were included in

TABLE 2 Respondents' demographics and genetic counseling practice characteristics

Demographics	<i>n</i> = 115	%
Gender		
Male	6	5.2%
Female	108	93.9%
Non-binary	1	0.9%
Race		
White (non-hispanic)	96	83.5%
White (hispanic)	11	9.6%
Asian	5	4.3%
Not specified	3	2.6%
Institution of employment		
Diagnostic laboratory (commercial, academic)	2	1.7%
Diagnostic laboratory (commercial, nonacademic)	8	7.0%
Government organization	3	2.6%
Physician's Private Practice	6	5.2%
Private hospital/medical center	28	24.3%
Public hospital/medical center	28	24.3%
University Medical Center	40	34.8%
Percent of time GCs see cancer indications		
0%	6	5.2%
1%–25%	8	7.0%
26%–50%	7	6.1%
51%–75%	12	10.4%
76%–100%	77	67.0%
I do not see patients	5	4.3%
Percent of time GCs see colon cancer indications		
0%	6	5.2%
1%–25%	72	62.6%
26%–50%	28	24.3%
51%–75%	3	2.6%
76%–100%	0	0.0%
I do not see patients	6	5.2%
Cancer genetics experience		
<5 years	68	59.1%
5 or more years	47	40.9%

the dataset. Descriptive statistics were used to describe the dataset.

3 | RESULTS

3.1 | Demographics

Of the 115 completed surveys, demographic variables reflect the current NSGC membership (Table 2). The

majority ($n = 96$, 84%) of respondents self-identified as non-Hispanic white females ($n = 108$, 94%). Most respondents practiced in the United States of America ($n = 113$, 98%), with 89% ($n = 102$) of respondents working in a clinical setting. While 77% ($n = 89$) of respondents reported cancer as their primary specialty, 59% ($n = 68$) had <5 years cancer genetic counseling experience. Respondents represented 30 different graduate training programs, with 73% ($n = 84$) graduating from their training program between 2010 and 2018.

3.2 | GC Management Practices

In response to the first pedigree (Figure 1a), 84% ($n = 96$) of GCs would not recommend LS CRC screening management if the unaffected proband had a negative genetic test (Figure 2a). Instead, 83% ($n = 95$) would recommend screening based on the family history of CRC. Twenty-seven percent ($n = 31$) would consider EC screening (Figure 2b), while 85% ($n = 98$) would not recommend screening for extra-colonic LS-related cancers (Figure 2c).

For pedigree 2 (Figure 1b), 96% ($n = 110$) of respondents would not elect LS CRC screening recommendations (Figure 2a). However, 52% ($n = 60$) suggested CRC screening should begin at 35 years, while 43% ($n = 50$) suggested CRC screening should begin at 50 years. Only 13% ($n = 15$) would consider EC screening (Figure 2b) and 5% ($n = 6$) would recommend extra-colonic screening (Figure 2c). Of the 89 individuals reporting cancer as their primary specialty (>51% of their time), 48% ($n = 43$) suggested colon screening beginning at 50 years while 69% ($n = 18/26$) of GCs that spent ≤50% of their time counseling for hereditary cancer suggested beginning screening at 35 years.

In the third case (Figure 1c), 83% ($n = 95$) of GCs would recommend CRC screening based on the family history of CRC (Figure 2a). With regard to EC screening, 96%, ($n = 110$) (Figure 2b) would make no specific recommendations. Ninety-four percent ($n = 109$) of GCs would not recommend extra-colonic LS-related screening (Figure 2c).

For pedigree 4 (Figure 1d), 84% ($n = 97$) of GCs would follow general population screening for CRC (Figure 2a) and 88% ($n = 101$) would consider EC screening (Figure 2b). However, 15% ($n = 17$) of GCs would recommend earlier CRC screening (Figure 2a) and 5% ($n = 6$) would recommend extra-colonic screening (Figure 2c).

For the final pedigree (Figure 1e), 32% ($n = 37$) of respondents would recommend LS CRC screening for the proband (Figure 2a), and would consider EC screening ($n = 37$) (Figure 2b). Extra-colonic LS-related screening would be recommended by 27% ($n = 31$) of respondents (Figure 2c).

When asked about the most appropriate provider to make screening recommendations for individuals who test negative

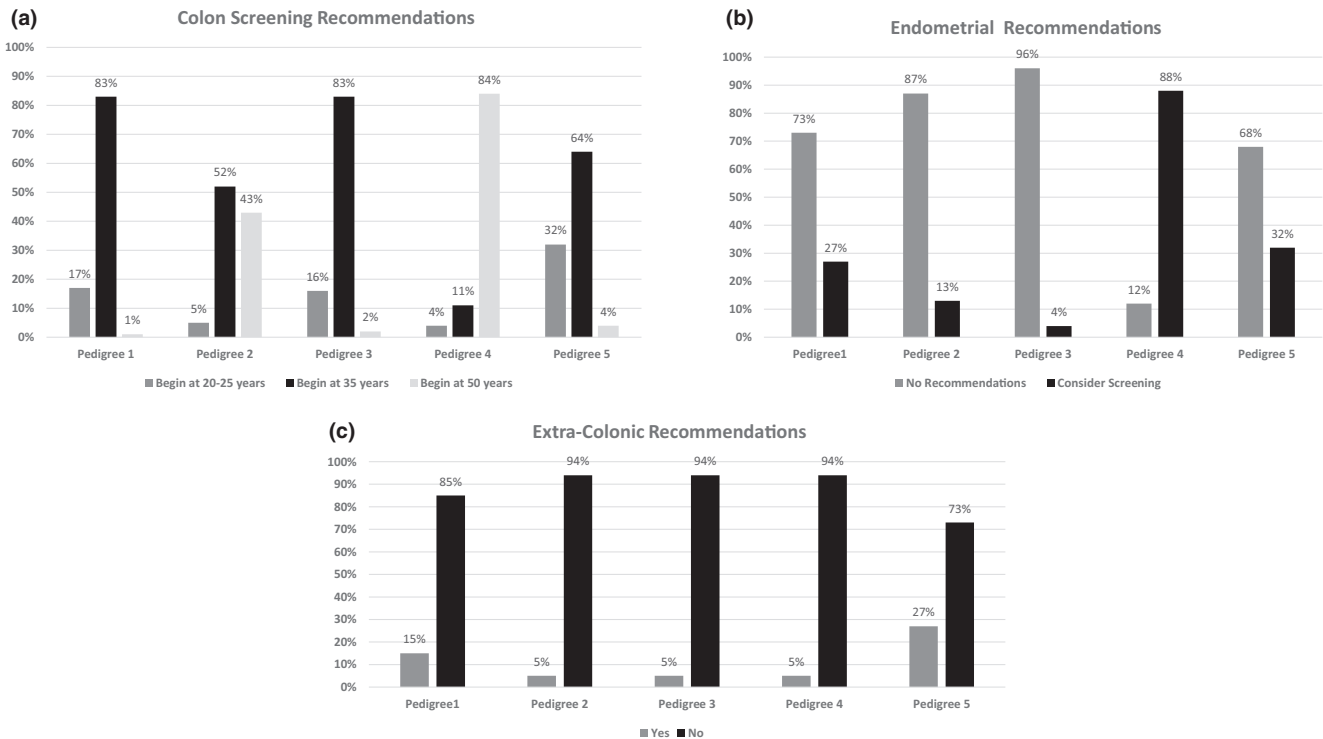


FIGURE 2 Respondents' screening recommendations for each hypothetical pedigree. (a) genetic counsellor (GC) recommendations for colorectal cancer screening including LS screening (begin colonoscopy at 20–25 years), family history-based screening (begin colonoscopy at 35 years) and general population screening (begin colonoscopy at 50 years). (b) GC recommendations for endometrial cancer screening including consider screening (via endometrial biopsy every 1–2 years and/or transvaginal ultrasound and consider hysterectomy after childbearing is complete) and no specific recommendations. (c) GC recommendations for extra-colonic screening

for LS with a suggestive family history, a little over half indicated specialty clinicians (54%, $n = 62$). This was followed by certified GCs (43%, $n = 43$) then primary care providers (2%, $n = 2$).

4 | DISCUSSION

Overall, there was a high level of agreement among GCs regarding management of individuals with negative genetic testing and family histories suggestive of LS. A majority of GCs agree that patients with complex family histories of EC and CRC do not need to follow LS screening guidelines; instead they recommend screening based on family history. As per NCCN, individuals with a first-degree relative (FDR) with CRC should begin colonoscopy screening at age 40, or 10 years before the earliest diagnosis of CRC in the family (Gupta et al., 2017) (Table 1). In the outlined scenario of pedigree 1 (Figure 1a), this would indicate screening should begin at 35 years. In the presence of guidelines, appropriate for the clinical scenario, GCs follow NCCN guidelines when making their medical management recommendations. Notably, even in the absence of guidelines for a specific clinical scenario, GCs are using their risk assessment skill set and agree on medical

management, as demonstrated by EC screening recommendations in pedigree 4 (Figure 2b).

An exception to the agreement among GCs was CRC screening recommendations in pedigree 2 (Figure 1b), specifically regrading at what age to begin screening. Over half of GCs (52%) suggested that CRC screening should begin at 35 years. Based on the NCCN family history CRC screening guidelines, individuals with a second-degree relative with CRC, regardless of age, should begin screening at age 50 (Gupta et al., 2017) (Table 1). While GCs who reported cancer as their primary specialty were more likely to suggest screening at age 50, this recommendation represented less than half of primary cancer GCs in this study. In scenarios with more complex family histories, this suggests that the majority of GCs may use clinical judgment instead of NCCN guidelines to recommend a more conservative CRC screening regimen.

The degree of relationship of the affected family members to the proband appears to affect screening recommendation. For example, pedigree 1 (Figure 1a) and pedigree 2 (Figure 1b) contain the same cancer types, but the affected individuals are of different degrees of relationship to the proband. Both have a second-degree relative affected with EC. However, in pedigree 1, a FDR is also affected with CRC. Respondents were more likely to recommend EC screening for the proband in pedigree 1 compared to pedigree 2

(Figure 2b), suggesting that as the degree of relationship of affected family members becomes further removed, respondents become less conservative in their recommendations. In reference to CRC screening recommendations, 83% of respondents would recommend beginning CRC screening at age 35 for pedigree 1, which follows NCCN family history CRC screening guidelines (Figure 2a). This drops to 52% in response to pedigree 2, where only second-degree relatives have been diagnosed with CRC. This effect may be due to decreased concerns surrounding CRC risk for the proband, or may be a reflection of NCCN family history CRC screening guidelines, which recommend CRC screening at age 50 for a family history of a second-degree relative with CRC.

When there is a family history of a single type of cancer, CRC (pedigree 3) or EC (pedigree 4), the majority of respondents would follow NCCN family history based CRC screening guidelines (Figure 2a). However, several respondents (88%) would consider EC screening for the proband in pedigree 4 (Figure 1d, Figure 2b). Interestingly, at this time, NCCN does not have family history based EC screening guidelines. While these scenarios reflect the use of NCCN family history based CRC screening guidelines, EC and extra-colonic screening recommendations appear to be based on clinical judgment, in light of the family history of cancer and the absence of guidelines.

Pedigree 5 (Figure 1e) highlights a clinical scenario with abnormal IHC and has the largest proportion of GCs recommending management similar to LS. This is interesting, given recent studies involving tumor testing that have shown in the absence of a germline pathogenic variant, abnormal IHC is most likely due to double somatic pathogenic variants (Haraldsdottir et al., 2014), rather than a germline pathogenic variant. However, at the time of survey administration, NCCN guidelines (v3.2017) suggested patients with single or no somatic pathogenic variant be followed as LS. Thus, GCs' responses were reflective of NCCN guidelines (v3.2017), not published data. It should be noted that NCCN management recommendations (v1.2018) based on tumor testing results have changed to reflect the current literature.

To our knowledge, this study is the first of its kind to query practice habits of GCs when managing families with complex family histories of CRC and EC. The use of pedigree-based clinical scenarios provided the opportunity to gauge how the degree of relation changes management recommendations among families. This study also highlights the highly unified responses in regard to risk assessment and management by GCs in the absence of guidelines that fit the clinical scenario. Lastly, recent studies have focused attention on the use of tumor testing to clarify the likelihood of LS, and therefore potential screening recommendations. This study reflects those cases where tumor testing is not an option (perhaps due to a lack of tumor sample or insurance/cost

barriers) and demonstrates how GCs handle these real-case scenarios.

Limitations to this study may have affected the study findings and the generalizability to the genetic counseling workforce. Study participants were recruited through the Cancer SIG and general NSGC discussion forums, leading to a sampling bias of cancer GCs. In addition, GCs who are members of the Cancer SIG and who receive discussion forum posts may be more likely to stay abreast of updated guidelines and screening recommendations. While this study is the first of its kind, a small sample size limited the ability to determine if demographic responses were predictors of screening recommendations.

Additional studies are needed to further explore exceptions in consistent screening recommendations among GCs. Detailed qualitative interviews would help to elucidate the rationale for why certain screening recommendations were made. Comparative studies involving nongenetic counseling clinicians would help to determine if there are differences in recommendations due to specialty and training. Results of this study highlight areas where there may be a need for future national guideline development to aid in managing patients with complex family histories of CRC and EC. Awareness of the discrepancies between GC recommendations is a step toward more uniform patient management. We recommend that patients be made aware of the ambiguities around current management guidelines.

5 | CONCLUSION

This study is the first to investigate GC management of families with complex family histories of CRC and EC. The majority of GCs in this study agree that patients with complex family histories of CRC or EC do not need to follow LS screening guidelines; however, there are exceptions among GCs regarding the age at which CRC screening should begin. This study suggests the need for further national guideline development tailored to managing patients with complex family histories.

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CONFLICT OF INTEREST

All authors disclose that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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